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The organizers cordially welcome all participants to the International Symposium on Inhalation Toxicology

## ASSESSMENT OF INHALATION HAZARDS: INTEGRATION AND EXTRAPOLATION USING DIVERSE DATA

February 19 — 24, 1989

Hannover Medical School Hannover, Federal Republic of Germany

Sponsored by
International Life Sciences Institute
Hannover Medical School
Fraunhofer Institute of Toxicology and Aerosol Research
and
Federal Ministry for the Environment, Nature Conservation
and Nuclear Safety

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#### Overview

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#### The Symposium

The protection of public health from the effects of common environmental pollutants has often, in the past, been made difficult by the absence of many kinds of data. This symposium will provide an opportunity to analyze data from animal exposure studies and from human epidemiology studies for the purpose of assessing the risks posed by pollutants and establishing some standards for exposure limits. The symposium will address these issues by examining data related to arsenic, benzene, formaldehyde, 1,3-butadiene, environmental tobacco smoke, mineral fibers, asbestos, automotive exhaust emissions, and polycyclic aromatic hydrocarbons.

The programme is designed to follow up the successful meeting held in 1987, "The Design and Interpretation of Inhalation Studies and their Use in Risk Assessment". At the 1987 meeting, animal data from exposure to diesel exhaust were considered in detail, and this pollutant will be reviewed in the light of new epidemiological data. Benzene also will be reviewed in the light of new data on public exposure.

The purpose of this symposium is threefold: 1) to review data on specific substances, 2) to advance our understanding of how the "integration" of diverse data should be addressed and how disparate data from animal exposures and human epidemiology studies should be approached, and 3) to consider what general lessons may be derived from a review of particular materials and their effects. Every attempt has been made to achieve scientific balance throughout the programme.

#### **Proceedings**

The lectures resulting from the plenary sessions of this symposium will be published as a monograph by Springer-Verlag.

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#### About the Sponsors

## International Life Sciences Institute

The International Life Sciences Institute (ILSI) was established in 1978 as a scientific, non-profit foundation to promote co-operation among government, industry and the academic world and to further the understanding and resolution of health, nutrition and safety assessment issues. Through ILSI, scientific experts from the academic, public and industrial sectors collaborate on research and education programmes at national and international levels.

ILSI sponsors research, publishes monographs and organizes workshops and symposia that relate to this broad spectrum of issues. Organizations which have collaborated with ILSI in these activities include government agencies, university departments and professional societies. ILSI participates in the work of the World Health Organization International Programme on Chemical Safety, the Joint FAO/WHO Expert Committee on Food Additives and the Joint FAO/WHO Codex Alimentarius Commission and its subsidiary bodies.

The membership of ILSI includes more than 140 food, chemical and pharmaceutical companies and associations in Australia, Europe, Japan and North America. Scientists from these organizations, as well as several hundred scientists from universities and government agencies, participate in ILSI programmes.

The activities of ILSI are based on the premise that, through co-operative programmes, scientists from industry, government and universities can have a positive impact on public health and the public's awareness of factors that affect its health.

#### Hannover Medical School

The Hannover Medical School (MHH) encompasses all disciplines of a modern medical educational establishment. It combines science and research with extensive care for in-patients and out-patients in both medicine and dentistry. The MHH consists of central divisions, service units and central institutions which co-operate closely with one another. A high technical standard is maintained in all facilities.

Some of the MHH's particular fields of involvement are heart surgery in infants, children and adults, clinical cardiology including cardiac catheter laboratory; child cancer therapy; liver and kidney transplantation, child and adult dialysis including a training centre for home dialysis; high standards in dental surgery and care; accident surgery plus emergency helicopter and ambulance service; nuclear medicine with own reactor and cyclotron; biometry and medical informatics; biomedical and hospital technology.

The MHH employs a staff of around 4,500, 700 of whom are medical doctors and 1,300 directly involved in patient care. With 2,080 beds at their disposal, the MHH and its associated hospitals treat over 37,000 in-patients annually. In addition, over 115,000 patients are treated each year in out-patient clinics. The hospital has a student population of 3,500, including 400 dental students. The MHH is active in various research fields and to conduct its research work depends heavily on financial support from public and private sources.

## Fraunhofer Institute of Toxicology and Aerosol Research

The Fraunhofer Institute of Toxicology and Aerosol Research is one of 35 separate research institutes forming The Fraunhofer Society for the Advancement of Applied Research whose main headquarters are based in Munich.

The research topics at the Fraunhofer Institute of Toxicology and Aerosol Research in Hannover relate to all fields of natural and biomedical sciences that may be of importance for promoting human health protection or environmental conservation and improvement. Contract research and intramural projects selected under these aspects are targeted for the protection of the general well-being of man and his environment under the impact of our modern technologically oriented and industrialized society. Local analyses and status inventories designed to preserve and, where necessary, to improve environmental quality are the first steps in that direction. They serve to make sure that neither the environment will suddenly produce human health hazards nor the quality of the environment itself deteriorate. For this purpose, the Fraunhofer Institute of Toxicology and Aerosol Research cooperates with industrial companies and public authorities in detecting, monitoring and reducing sources of harmful emissions, particularly in the air pollution field, in tracing health risks of old and new chemical substances and in developing processes, products and test procedures compatible with and relevant to the environment. The interdisciplinary structure of the institute facilitates a diversified teamwork approach in research areas where aspects of medicine, biology, chemistry and physics overlap. With these objectives and an adequate staff structure, the institute represents a place of experimental contract research suitable for dialogues between industry and government including supranational and international organizations.

#### Addresses of Sponsoring Organizations

For more information about the sponsoring organizations, please contact:

Ms. Sharon Senzik International Life Sciences Institute 1126 Sixteenth Street, NW, Suite 300 Washington, DC 20036, USA Tel: (202) 659-0789

Prof. Dr. Ulrich Mohr Hannover Medical School Institute of Experimental Pathology Konstanty-Gutschow-Str. 8 3000 Hannover 61, FRG Tel: (0511) 532-4520

Prof. Dr. Werner Stöber Fraunhofer Institute of Toxicology and Aerosol Research Nikolai-Fuchs-Str. 1 3000 Hannover 61, FRG Tel: (0511) 5350-112

#### Acknowledgement of Financial Support

The Scientific Planning Committee wishes to thank all the organizations who have given generous donations to ILSI in support of the symposium.

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#### General Information

#### Location and Meeting-place

All lectures and poster sessions will be held at the Hannover Medical School. Registration and meeting-place will be in Building I 1, 2nd floor (see plan of the Medical School). The Plenary Sessions and Case Studies will be held in Lecture Hall F; afternoon paper sessions will run concurrently with each other in Lecture Halls F and M. Posters (see p. 27) will be presented in the vestibule.

#### **On-Site Demonstrations**

It will be possible for a limited number of participants to tour the Fraunhofer Institute of Toxicology and Aerosol Research which is situated next to the Medical School campus. For further information, please contact the information desk.

#### Assistance

If you need assistance or information on any matter, please contact one of the members of the secretariat.

If you wish to show slides with your paper presentation you are asked to call at our technical enquiry desk before the session in which you are due to speak.

#### Messages

Emergency messages can be telephoned to the symposium office on (0511) 532-5000.

## **Buffet Supper for all Participants**

On Thursday, 23rd February, 1989 all participants are invited to the Hotel Inter-Continental in Hannover for an evening with traditional country fare from the Lower Saxony region ("Niedersächsischer Dorfabend"). The buffet will begin at 6.30 p.m. Transport will be provided from the Medical School to the Hotel Inter-Continental which is centrally situated opposite the New Town Hall (Neues Rathaus). Buses will depart from outside the hotel at 9.30 p.m. to return participants to their respective hotels.

#### **Breaks and Lunch**

The registration fee includes the buffet supper on Thursday, 23rd February, 1989 and all refreshment breaks, excluding lunch. Lunches are served in the Medical School cafeteria, The Mensa (Building K I5, see plan of the Medical School). Lunch tickets can be purchased each day from the symposium office at a cost of DM 7.50 per meal.

## **Experimental Pathology**

Presenters of proffered papers and posters wishing to have their work published in the September 1989 issue of "Experimental Pathology" are reminded to hand in their manuscripts to Prof. Dr. F. Bolck, the journal's editor, before their departure. We regret that once the symposium is over manuscripts can no longer be accepted for publication.

#### Official Language

The official language of the symposium is English. A simultaneous translation service will be provided (English/German) in Lecture Hall F.

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#### Faculty

## John C. Bailar, M.D., Ph.D.

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#### Kurt Ulm, Dr. rer. nat.

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#### Marie Vahter, Dr. Med. Sc.

Karolinska Institute, Institute of Environmental Medicine, Stockholm, Sweden

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		The Symposi	um at a Glance		
Sunday 19 February	Monday 20 February	Tuesday 21 February	Wednesday 22 February	Thursday 23 February	Friday 24 February
	Registration 8.00 — 8.30	CASE STUDIES	CASE STUDIES	CASE STUDIES	PLENARY SESSION III 8.00 — 11.10
	Welcome and Introduction 8.30 — 9.00	Formaldehyde 8,00 — 10.15	Butadiene 8.00 — 10.15	Environmental Tobacco Smoke 8.00 — 10.15	Symposium Synthesis 11.10 — 12.10
	PLENARY SESSION I 9.00 — 10.20	Arsenic 10.50 — 12.20	Benzene 10.50 — 13.05	Automotive Exhaust Emissions & PAHs	Closing Remarks
	PLENARY SESSION II			10.50 — 13.05	Adjournment 12.20
	Epidemiological 10.50 — 12.10				
	Lunch 12.10 — 13.30	Lunch 12.20 — 13.30	Lunch 13.05 — 14.30	Lunch 13.05 — 14.00	
	Animal 13.30 — 14.50	Kenneth Morgareidge Award 13.30 — 14.00	Mineral Fibers 14.30 — 16.45	PAPER SESSION 14.00 — 17.45	
	Dosimetric 14.50 — 16.40	PAPER SESSION 14.00 — 15.30	POSTER SESSION 17.00 — 18.00		
Registration 17.00 — 19.00	Mechanistic 16.40 — 18.00	POSTER SESSION 16.00 — 17.00			
		PAPER SESSION 17.00 — 18.00	•	Buffet Supper 18.30	

All posters will be on display throughout the meeting. However, authors will be asked to be present with their posters during the specifically designated poster sessions. Please consult appendix for poster titles.

Sunday, 19 I	Sunday, 19 February (evening)
17.00 — 19.00	Registration
Monday, 20	Monday, 20 February (morning)
8.00 8.30	Registration  Welcoming Speeches (Lecture Hall F)  Prof. Dr. med. Klaus Alexander, Rector, Hannover Medical School  Dr. rer. pol. Werner Remmers, Minister of Environment of  Lower Saxony  Clemens Stroetmann, State Secretary, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety  Introduction and Announcements
PLENARY INTEGRAT TWO CONT Chairman:	PLENARY SESSION I: (Lecture Hall F) INTEGRATIVE APPROACH TO ASSESSING HUMAN HEALTH RISK: TWO CONTEMPORARY PROBLEMS Chairman: Carol J. Henry, Ph.D., D.A.B.T., ILSI Risk Science Institute
9.00	Integrating diverse data sets to assess the risks of airborne pollutants Roger O. McClellan, D.V.M., Chemical Industry Institute of Toxicology
9.40	Risk assessment for radon inhalation based on animal exposure data and human epidemiology Friedrich Steinhäusler, Prof. Dr. phil., University of Salzburg
10.20	Refreshment break
PLENARY TYPES OF	PLENARY SESSION II (Lecture Hall F) TYPES OF EVIDENCE: GENERAL STRENGTHS AND WEAKNESSES
Epidemiological Chairman: Jos	jical Jonathan M. Samet, M.D., University of New Mexico
10.50	Inhalation hazards: the interpretation of epidemiologic evidence John C. Bailar, M.D., Ph.D., McGill University and United States Department of Health and Human Services
11.30	Problems in interpreting epidemiological data Peter N. Lee, M.A., P.N. Lee Statistics and Computing Ltd
5	Lunch

Programme

Monday, 20	February (afternoon)
PLENARY	SESSION II (continued) (Lecture Hall F)
Animal	
Chairman:	Donald L. Dungworth, Ph.D., M.R.C.V.S., University of California, Davis
13.30	The use of animal studies in risk assessment Gary A. Boorman, D.V.M., Ph.D., National Institute of Environmental Health Sciences
14.10	The quality and relevance of data from studies in laboratory rodents Francis J.C. Roe, D.M., D.Sc., F.R.C.Path., Consultant in Toxicolog and Adviser in Experimental Pathology and Cancer Research
Dosimetric	
Chairman:	Werner Stöber, Prof. Dr. rer. nat., Fraunhofer Institute of Toxicology and Aerosol Research
14.50	Identification of the effective dose of inhaled toxicants: general and specific problems  Hermann M. Bolt, Prof. Dr. med., Dr. rer. nat., University of Dortmund
15.30	Refreshment break
16.00	Molecular dosimetry of chemical carcinogens: implications for risk assessment George W. Lucier, Ph.D., National Institute of Environmental Health Sciences
Mechanistic	2
Chairman:	Hans Marquardt, Prof. Dr. med., University Hospital Eppendorf
16.40	Human lung carcinogenesis: molecular mechanisms and epidemiology Curtis C. Harris, M.D., National Cancer Institute
17.20 — 18.00	A mechanistic approach to assess the inhalation toxicity and hazard of methylisocyanate and related aliphatic monoisocyanates Jürgen Pauluhn, DiplChem., Dr. rer. nat., Bayer AG

Tuesday, 21	February (morning)
CASE STU	DIES (Lecture Hall F)
Formaldehy	de
Chairman:	Curtis C. Harris, M.D., National Cancer Institute
8.00	Inhalation toxicity and carcinogenicity of formaldehyde in animals: significance for assessment of human health risk Victor J. Feron, Ph.D., TNO-CIVO Toxicology and Nutrition Institute
8.40	Formaldehyde: evidence of the carcinogenic potential from epidemiological data Kurt Ulm, Dr. rer. nat., Technical University Munich
9.20	Mechanisms of formaldehyde carcinogenesis  James A. Swenberg, D.V.M., Ph.D., Chemical Industry Institute of Toxicology
10.00	Synthesis
10.15	Refreshment break
Arsenic	
Chairman:	David V. Bates, M.D., University of British Columbia
10.50	Environmental and occupational exposure to arsenic Marie Vahter, Dr. Med. Sc., Karolinska Institute, Institute of Environmental Medicine
11.30	Integration of the inhalation and ingestion cancer risk data for arsenic Herman Gibb, M.P.H., United States Environmental Protection Agency
12.10	Synthesis

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12.20

Lunch

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Tuesday, 21	February (afternoon)		luesday, 2	February (afternoon)
13.30	(Lecture Hall F)		PAPER SE	SSION: Animal (Lecture Hall M)
	Presentation of the 1989 KENNETH MORGAREIDGE AWARD by Dr. Alex Malaspina, President of the International Life Sciences Institute, to this year's winner, Dr. Melvin E. Andersen. Following the presentation Dr. Andersen will give a short talk on his work.	*	Chairman:	Gary A. Boorman, D.V.M., Ph.D., National Institute of Environmental Health Sciences
concurrently	ternoon paper sessions on Animal and Dosimetric Data will run with the paper session on Automotive Exhaust.	,	14.00	Carcinogenic risk by methylene chloride inhalation: low-dose extrapolation by animal experiments  A.R. Bucchi, A. Loizzo, P. Valente and G.A. Zapponi, Istituto Superiore di Sanitá, Rome, Italy
	SSION: Automotive Exhaust (Lecture Hall F)			
Chairman:	Roger O. McClellan, D.V.M., Chemical Industry Institute of Toxicology  Ambient air concentrations of diesel particulate matter		14.15	Determination of concentration-time-mortality relationships instead of LC50 according to OECD guideline 403 increases information content without the need for more animals
	D. Schürmann, Volkswagen AG, Wolfsburg, FRG			J.H.E. Arts, A. Zwart, E.D. Schoen, J.M. Klokman-Houweling, TNO-CIVO, Zeist and TNO-ITI, Delft, The Netherlands
14.15	Diesel particulate emission in West Germany N. Metz, BMW AG, Munich, FRG			
14.20	Reversible fraction of airway resistance in healthy children of areas		PAPER SE	SSION: Dosimetric (Lecture Hall M)
14.30	with different levels of atmospheric pollutants  M.S. Islam and HW. Schlipköter, Medical Institute of Environmental Hygiene, University of Düsseldorf, Düsseldorf, FRG		Chairman:	Francis J.C. Roe, D.M., D.Sc., F.R.C.Path., Consultant in Toxicology and Adviser in Experimental Pathology and Cancer Research
14.45	Comparative long-term animal inhalation studies using various particulate matter: objectives, experimental design and preliminary results U. Heinrich, R. Fuhst, L. Peters, H. Muhle, C. Dasenbrock and F. Pott, Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, FRG	~	14.30	The metabolic behaviour of uranium octoxide bearing residues after their deposition in the rat lung: the implications for occupational exposure  G.N. Stradling, J.W. Stather, S.A. Gray, J.C. Moody and  A. Hodgson, National Radiological Protection Board, Chilton, Didcot, Oxon, UK
15.00	Diesel exhaust exposure and lung cancer R.E. Harris, P. Boffetta and E.L. Wynder, American Health Foundation, New York, NY, USA	<b>h.</b>	14.45	The efficacy of pure LICAM (C) and DTPA for enhancing the elimination of plutonium and americium inhaled as their nitrates G.N. Stradling, J.W. Stather, S.A. Gray, J.C. Moody, A. Hodgson and M. Ellender, National Radiological Protection Board, Chilton,
15.15	Dust overloading causes impairment of pulmonary clearance: evidence from rats and humans			Didcot, Oxon, UK
	J.N. Pritchard, Environmental and Medical Sciences Division, Harwell Laboratory, Oxon, UK		15.00	Inhalation reference dose for insoluble particles: dosimetric adjustments affect the selection of animal model
15.30	Refreshment break			A.M. Jarabek <sup>1</sup> , M.G. Menache <sup>2</sup> . F.J. Miller <sup>1</sup> , <sup>1</sup> US Environmental Protection Agency; <sup>2</sup> NSI Technology Services Corporation, Research
16.00 — 17.00	POSTER SESSION			Triangle Park, NC, USA

## Tuesday, 21 February (afternoon)

The Tuesday afternoon paper session on Mineral Fibers and Particles will run concurrently with the paper session on Butadiene and Formaldehyde.

#### PAPER SESSION: Mineral Fibers and Particles (Lecture Hall F)

I THE DAY OF	DIO: IMMerca I toolo and I are noted (Double of Anni I)
Chairman:	Friedrich Pott, Prof. Dr. med., Medical Institute of Environmental Hygiene, University of Düsseldorf
17.00	The effect of fibre durability on the hazard potential of inhaled chrysotile asbestos fibres  A.D. Jones, J.H. Vincent, C. McIntosh, C. McMillan and J. Addison Institute of Occupational Medicine, Edinburgh, UK
17.15	Comparative study of quartz dust induced cytotoxicity on rodent and human macrophages  H. Behrendt, N. Seemayer and R. Ziesche, Medical Institute of Environmental Hygiene, University of Düsseldorf, Düsseldorf, FRG
17.30	Lung tumor induction upon long-term low-level inhalation of crystalline silica  H. Muhle <sup>1</sup> , S. Takenaka <sup>1</sup> , U. Mohr <sup>1</sup> , C. Dasenbrock <sup>1</sup> and R. Mermelstein <sup>2</sup> , 'Fraunhofer Institute of Toxicology and Aerosol Research, Hannover, FRG; 'Corporate Environmental Health and Safety, Xerox Corp, Rochester, NY, USA
17.45 —	Environmental pulmonary mineral particles correlated with smoking,

# 17.45 — Environmental pulmonary mineral particles correlated with smokin emphysema and lung cancer P.-L. Kalliomäki<sup>1</sup>, O. Taikina-aho<sup>2</sup>, P. Pääkkö<sup>2</sup>, S. Sivonen<sup>2</sup>, K. Kalliomäki<sup>2</sup> and S. Antila<sup>1</sup> Unstitute of Occupational Health

K. Kalliomäki<sup>2</sup> and S. Anttila<sup>1</sup>, 'Institute of Occupational Health, Helsinki, Finland; 'Institute of Electron Optics, Department of Pathology and Laboratory of Measuring Technique, University of Oulu, Oulu, Finland

## PAPER SESSION: Butadiene/Formaldehyde (Lecture Hall M)

Chairman:	Hermann M. Bolt, Prof. Dr. med., Dr. rer. nat., University of
	Dortmund
17.00	

17.00 Determination of benzene and 1,3-butadiene in cigarette smoke by CG-MSD K.D. Brunnemann, M. Kagan and D. Hoffmann, American Health

Foundation, Valhalla, NY, USA

17.15 The paradox of butadiene epidemiology
J.F. Acquavella, Exxon Biomedical Sciences Inc, East Millstone,
NJ, USA

Quantitative risk approaches for formaldehyde C.T. Howlett, R. Mathias and S. Friess, Georgia-Pacific Corporation, Washington, DC, USA

17.45 — Reanalysis of lung cancer mortality in a National Cancer Institute
18.00 study on "mortality among industrial workers exposed to formaldehyde"
T.D. Sterling and J.J. Weinkam, Simon Fraser University, Burnaby,
BC, Canada

## Wednesday, 22 February (morning)

## CASE STUDIES (Lecture Hall F)

Butadiene	
Chairman:	Hermann M. Bolt, Prof. Dr. med., Dr. rer. nat., University of Dortmund
8.00	Toxicology and carcinogenicity of 1,3-butadiene Ronald L. Melnick, Ph.D., National Institute of Environmental Health Sciences
8.40	Species differences in pharmacokinetics, metabolism and DNA-binding of inhaled 1,3-butadiene Reinhold J. Laib, Dr. rer. nat., University of Dortmund
9.20	Epidemiologic data related to health effects of 1,3-butadiene Genevieve M. Matanoski, M.D., Ph.D., The Johns Hopkins University
10.00	Synthesis
10.15	Refreshment break
Benzene	
Chairman:	Bernard Goldstein, M.D., Robert Wood Johnson School of Medicine
10.50	A review of the toxicokinetics of benzene Michele A. Medinsky, Ph.D., Lovelace Inhalation Toxicology Research Institute
11.30	Benzene: a multipotential experimental carcinogen Cesare Maltoni, M.D., Institute of Oncology, Bologna
12.10	Benzene haematotoxicity and leukaemia Allan Jacobs, M.D., F.R.C.Path., University of Wales College of Medicine
12.50	Synthesis
13.05	Lunch

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17.30

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## Wednesday, 22 February (afternoon)

## CASE STUDIES (Lecture Hall F)

## Mineral Fibers

Chairman:	Lorenzo Tomatis, M.D., International Agency for Research on Cancer
14.30	Exposure assessment for man made mineral fiber
	Morton Corn, Ph.D., The Johns Hopkins University
15.10	The carcinogenicity of fibers in animals — data and evaluation
	Friedrich Pott, Prof. Dr. med., University of Düsseldorf
15.50	The health effects of man-made mineral fibers
	Rodolfo Saracci, M.D., International Agency for Research on Cancer
16.30	Synthesis
16.45	Refreshment break
17.00 —	POSTER SESSION
18.00	

## Thursday, 23 February (morning)

## CASE STUDIES (Lecture Hall F)

## **Environmental Tobacco Smoke**

Chairman:	David V. Bates, M.D., University of British Columbia
8.00	Environmental tobacco smoke (ETS): adverse effects on respiratory infection, respiratory symptoms, and lung function Jonathan M. Samet, M.D., University of New Mexico
8.40	Environmental tobacco smoke and cancer — assessment of the evidence Göran Pershagen, M.D., Ph.D., Karolinska Institute, Institute of Environmental Medicine
9.20	Risk assessment for inhomogeneous subgroups Berthold Schneider, Prof. Dr. rer. nat., Hannover Medical School
10.00	Synthesis .
10.15	Refreshment break
Automotive	Exhaust Emissions and Polycyclic Aromatic Hydrocarbons
Chairman:	Roger O. McClellan, D.V.M., Chemical Industry Institute of Toxicology
10.50	Epidemiologic studies of occupational exposure to polycyclic aromatic hydrocarbons Marc B. Schenker, M.D., M.P.H., University of California, Davis
11.30	Exhaust specific carcinogenic effects of PAH and their significance for the estimation of the exhaust-exposure-related lung cancer risk Uwe Heinrich, Dr. rer. nat., Fraunhofer Institute of Toxicology and Aerosol Research
12.10	Molecular dosimetry of inhaled diesel exhaust James A. Bond, Ph.D., Lovelace Inhalation Toxicology Research
	Institute
12.50	

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